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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

KUBELIK, ANNE R

ART UNIT	PAPER NUMBER
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1638

8

DATE MAILED: 06/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application N .

09/807,722

Examiner

Anne R. Kubelik

Applicant(s)

DANIELL, HENRY

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 March 2003 and 09 January 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-32 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on with the application is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

1. Claims 1, 5-6, 8-10, 14-28 and 30 have been amended, claims 11-12 and 29 have been cancelled, and claim 31 has been added, as requested in Paper No. 6, filed 9 January 2003 and the claims have been amended as requested in Paper No. 7, filed 24 March 2003.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. The filing date to one of the provisional applications to which the instant application claims priority remains incorrectly identified in the declaration and in the first paragraph of the specification. In the response filed 9 January 2003 Applicant urges that priority has been corrected (response pg 9). This is not found persuasive because the information in the declaration and first paragraph of the specification remains in error. A amendment was made to the first paragraph of the specification; priority is now claimed to a provisional application filed in 1998 and not drawn in any way to chloroplast transformation and for which Henry Daniell, the inventor of the instant application, is not a listed inventor. Furthermore, no corrected oath/declaration was filed.

The provisional application is to which priority was originally claimed is 60/208,763; it is correct filing date is 6/2/2000. In the declaration its filing date is incorrectly listed as 6/6/2000.

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because of the errors in claiming benefit of a provisional application as indicted above.

Response to Arguments

5. The 35 USC 103 rejections of claims 1-12, 14-17, 19-25, 27-28 and 30 as being unpatentable over Maliga et al in view of Holmstrom et al (1994, Plant Journal 6:749-758), and claims 1-12, 14-17, 19-28 and 30 as being unpatentable over Maliga et al in view of each of Ursin (1997, US Patent, 5,633,153) and Rathinasabapathi et al (1994, Planta 193:155-162) is withdrawn in favor of the rejection below.

Claim Objections

6. Claims 4, 8-9, 19-23 and 25-26 are objected to because of the following informalities:

Claims 4, 8 and 23 have an improper article at the start of the claim.

Claim 8 has the misspellings "proprionaldehyde" and "butyraladehyde" in line 3.

An article is missing before "higher" in claim 9, line 2.

A comma is missing after "aldehyde" in claim 9, line 2.

In claim 19, an article is missing before "plastid" in line 1 and before "detoxifying" in line 2.

Claim 20 is missing a period at the end of the claim.

Claims 21-22 are missing a comma after "19".

In claim 25, line 2, the comma before "betaine" should be deleted.

In claim 26, the comma after "beet" should be deleted.

Claim Rejections - 35 USC § 112

7. Claims 1-28, 30 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a plastid transformation vector encoding betaine aldehyde dehydrogenase (BADH), a method for transforming tobacco plants with it, and tobacco plants so transformed, does not reasonably provide enablement for a plastid transformation vector for transforming all plant species, plastid transformation vectors encoding other phytotoxin detoxifying enzymes, methods of transforming the plastid of any plant, or a plant of any species whose plastids have been transformed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is repeated for the reasons of record as set forth in the Office action mailed 3 September 2002, as applied to claims 1-12, 14-17, 19-28 and 30. Applicant's arguments filed 9 January 2003 and 24 March 2003 have been fully considered but they are not persuasive.

Applicant urges that the specification is enabling and that the experimentation required must only not be undue. Applicant urges that Ursin (US Patent 5,633,153) was given a patent to genus covering a DNA sequence encoding aldehyde dehydrogenase; thus, the instant application is enabled (responses, 9 January 2003, pg 10, and 24 March 2003, pg 7-8).

This is not found persuasive. Examiner cannot comment on an issued patent. However, it is the instant application that must provide an enabling disclosure (see *Genentech, Inc. v. Novo Nordisk, A/S*, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997)). The specification does not teach other DNA sequences that encode enzymes that detoxify phytotoxins or other aldehyde dehydrogenases; thus, the instant specification is not enabling.

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Applicant urges that the specification incorporates by reference to WO 99/10513 a universal vector that transforms the plastid genome of different plant species (responses, 9 January 2003, pg 11-12, and 24 March 2003, pg 8-10).

This is not found persuasive because Heifetz, cited in the prior Office action, teaches that plastid transformation and regeneration of fertile plants with transformed plastids is limited to two plant species. Note that newly added claim is drawn to progeny of the plant; thus, fertility is required. None of the plants transformed in WO 99/10513 produced seeds and most were not regenerated into plants; thus, WO 99/10513 cannot be relied on for enablement.

Applicant urges that at the time the instant application was filed there were at least 60 known transcriptionally active spacer regions from higher plants plastid genomes. Applicant cites Sugita et al (1996). Applicant, citing Ruf et al (2001), and Sidirov et al (1999), states that the plastids of tomato and potato have been transformed. Applicant urges that Heifetz teaches that complete plastid genomes have been sequenced and urges that this information can provide information on conservation of reading frames and regulatory sequences. Applicant lists a variety of plants and states that their genome sequences were available in GenBank at the time of filing. Applicant urges that one could simply search appropriate spacer regions of the various plastid genomes without undue experimentation (responses, 9 January 2003, pg 12-14 and 24 March 2003, pg 10-12).

This is not found persuasive. Sugita et al (1996), Ruf et al (2001), Sidirov et al (1999) and the Genbank sequences could not be considered because they were not sent. However, Heifetz and Ruf et al (2001) cannot be relied on for enablement because they were published after the filing date of the instant application (see *In re Glass*, 181 USPQ 31, 34 (CCPA 1974),

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which teaches that references published after the filing date of an application may not be relied upon for the enablement of the specification.) Furthermore, Heifetz indicates that stable plastid transformation requires regeneration of fertile plants with transformed plastids (pg 656, left column, paragraph 1) and that segregation to the homoplastic state is the factor limiting plastid transformation to solanaceous plants (pg 658, right column, paragraph 2). Knowledge of DNA sequences does not provide overcome these problems and does not enable plastid transformation.

Applicant urges that Example 18 of the Written Description Guidelines correlates with Applicant's claims relating to selecting genetically engineered plants without use of antibiotics and urges that example 18 is drawn to an allowed genus even though only one embodiment was reduced to practice (responses, 9 January 2003, pg 14-15, and 24 March 2003, pg 12-13).

This is not found persuasive because Example 18 of the Written Description Guidelines is drawn to Written Description, not enablement. See the Written Description rejection below.

Applicant urges that [nucleic acids encoding] any of a variety of detoxifying enzymes could be inserted in to the plastid and tested for expression with a corresponding phytotoxic aldehyde (responses, 9 January 2003, pg 15, and 24 March 2003, pg 13).

This is not found persuasive. The specification must teach the nucleic acids encoding the enzymes, and it fails to do so. The specification does not teach which of the multitude of detoxifying enzymes are suitable for use as a selectable marker. The teachings of the specification does not teach the full scope of the claimed genus.

Applicant urges that pg 9, lines 11-17 of the specification, Fig. 9A and 9B and references incorporated by reference teach vectors besides PLD-BADH (responses, 9 January 2003, pg 15, and 24 March 2003, pg 13).

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This is not found persuasive because in Figures 9A-B structures like "Alfalfa CT Border" et al are not described at all - what is this? Additionally, none of these Figures nor the references teach nucleic acids encoding detoxifying enzymes other than BADH.

8. Claims 1-28, 30 and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is repeated for the reasons of record as set forth in the Office action mailed 3 September 2002, as applied to claims 1-12, 14-17, 19-28 and 30. Applicant's arguments filed 9 January 2003 and 24 March 2003 have been fully considered but they are not persuasive.

Applicant urges that Example 18 of the Written Description Guidelines correlates with Applicant's claims relating to selecting genetically engineered plants without use of antibiotics. Applicant urges that in the example only one gene of interest was illustrated and their own example using only a vector encoding BADH is similarly representative of the claimed genus. (responses, 9 January 2003, pg 14-15, and 24 March 2003, pg 12-13).

This is not found persuasive. Example 18 of the Written Description Guidelines is not analogous to the instantly case. Example 18 is drawn to a method of using a vector encoding any protein; vector components are not the critical part of the method. The instant claims are drawn to vectors and plants as well as methods, and the instant vectors and methods require that the detoxifying enzymes be suitable for use as a selectable marker for plastid transformation. For the instantly claimed vectors, plants and methods to be described, the components of the vectors, which are critical to the invention, must be described. They are not. The "spacer regions" are

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not described in terms of structure and function and nucleic acids encoding detoxifying enzymes other than BADH are also not described in terms of structure and function. Thus, the claimed plants and methods are also not described.

9. Claims 1-11, 14-28 and 30-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections. The rejection is repeated for the reasons of record as set forth in the Office action mailed 3 September 2002, as applied to claims 1-12, 14-17, 19-28 and 30. Applicant's arguments filed 9 January 2003 and 24 March 2003 have been fully considered but they are not persuasive.

The following rejections are new or remain and were not addressed in the responses:

Claims 1 and 9 are indefinite in their recitation of "higher plant species" in line 2. It is unclear what plants are considered "higher".

Claim 1 is indefinite in its recitation of "wherein said ... vector is contained in an expression cassette" in lines 3-4. Expression cassettes do not contain vectors, although vectors may comprise expression cassettes.

Claims 1, 9 and 19 remain and claim 31 is indefinite in their references to spacer regions and spacer sequences. It is unclear what a spacer region or sequence is and it is unclear what it means to be inclusive of a spacer region or sequence.

It remains unclear in claim 1, lines 4-5, claim 9, line 5, and claim 19, line 5, and is unclear in claim 31 to what the phrase "a 5' part of a plastid DNA sequence" refers. It is not clear to which plastid sequence the part is 5'.

Claim 1, lines 6-7, claim 9, line 6, and 31, lines 5-6 are indefinite in their recitation of "which is capable of ...". It is unclear what the phrase is intended to modify. By position in the claim it modifies "marker" - is it intended to modify "enzyme"?

Claim 1 lacks antecedent basis for the limitation "the spacer sequence" in lines 9-10.

It remains unclear in claim 1, line 9, claim 9, line 10, and claim 19, line 10, and is unclear in claim 31 to what the phrase "a 3' part of a plastid DNA sequence" refers. It is not clear to which plastid sequence the part is 3'.

Claim 2, line 2, claim 9, line 7, and claim 31, lines 6-7, are indefinite in their recitation of "heterologous DNA sequence". It is unclear to what the DNA is heterologous - the vector? the promoter?, the DNA sequence encoding a detoxifying enzyme?

It is unclear in claims 2 and 20 where the heterologous DNA sequence is located on the vector relative to the other components of the vector.

It remains unclear in claims 3 and 30 where the ribosome binding site and the 5' UTR are located on the vector relative to the other components of the vector. In claim 30 is also unclear whose expression is enhanced.

Claim 4 lacks antecedent basis for the limitation "the detoxifying ... protein" in line 2.

Claims 5-6 lack antecedent basis for the limitation "The chloroplast vector of claim 2".

Claim 8 lacks antecedent basis for the limitation "A vector of claim 4 for stably transforming the chloroplast genome".

In claims 8 and 31, it is not clear what the phrase "where growth aldehyde in line 2 is intended to modify - the genome? the vector? Neither make sense since neither "grow".

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Claim 18 is indefinite in its recitation of “wherein the selectable marker driven by a promoter”. Words, possibly --expression of--, appear to be missing before “selectable”.

Claim 18 is indefinite in its recitation of “tissues selected from the group consisting of ... the accD promoter” in line 2-4. Promoters are not tissues. The Markush group should list green and non-green tissues. If Applicant intends that the Markush group refer to the promoters that can drive the expression of the selectable marker, --, wherein the promoter is-- should be inserted after “tissues”.

Claim 20, line 2, is indefinite in their recitation of “heterologous target DNA sequence”. It is unclear to what the DNA is heterologous and for what it is a target.

Claim 22 lacks antecedent basis for the limitation “the phytotoxic aldehyde” in line 1.

Claim 23 lacks antecedent basis for the limitations “said phytotoxic aldehyde” in line 2 and “the DNA encoding sequence” in line 3.

Claim 23 is indefinite in their recitation of “selecting a plant cell that has the DNA ... introduced”. Words appear to be missing or in the wrong order; the current wording is awkward. One can select a plant cell that comprises a particular DNA or can select a plant cell into which a DNA has been introduced.

Claim 24 lacks antecedent basis for the limitation “said transformed plant cells”.

Claim 25 is indefinite in its recitation of “said phytotoxic aldehyde and the aldehyde dehydrogenase is ... (BADH).” It is unclear if both the aldehyde and the dehydrogenase are BADH or if words are missing. If the former, “is” should be --are--; it would be then unclear how an enzyme can be an aldehyde.

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Claim 28 is indefinite in its recitation of the members of the group. Those members are genes, not promoters. It is suggested that --from a gene-- be inserted before "selected" in line 1.

In claim 31 is indefinite in its recitation "a phytotoxic aldehyde". Is this phrase intended to modify "betaine aldehyde" (which would inherently be a phytotoxic aldehyde) or are words missing from the claim?

Claim 31 is indefinite in its recitation of the phrase beginning with "which comprises" in line 2. It is unclear what the phrase is intended to modify - phytotoxic aldehyde? betaine aldehyde? genome? vector? By position in the claim it modifies "phytotoxic aldehyde".

Claim 31 lacks antecedent basis for the limitation "said tobacco plastid" in line 8.

It is unclear in claim 32 if the progeny comprise the vector with which the stably transformed plant has been transformed. If the plant of claim 10 is used as the male parent, none of its progeny will comprise the vector with which its parent has been transformed.

10. Claim 7 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. This claim is an omnibus type claim. Applicant did not address this rejection in the responses filed 9 January 2003 and 24 March 2003.

11. Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The method further comprises culturing the plant in plant growth medium; however, in parent claim 19, no plant is produced. In claim 19, the only step is introducing a vector into plant cells. The omitted steps are those required to regenerate a plant from the plant cells.

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Furthermore, a later step in claim 23 recites selecting a plant cell - did Applicant intended that a cell be selected from the plant or should "plant" in line 1 be replaced with --cells--?

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 1-3, 5-6, 18-20, 28 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Blowers et al (WO 99/05265).

Blowers et al teach plant plastid transformation vectors comprising a region of homology to the petunia plastid genome (the ORF70B gene), the petunia plastid 16S rRNA promoter, a ribosome binding site in a 5' untranslated leader, a DNA sequence encoding a detoxifying enzyme (hph or glpB), a DNA sequence encoding a protein of interest (aadA), the transcription termination region from the *psbA* gene and another a region of homology to the petunia plastid genome (the *trnV*-16SrDNA-*trnI* genes) (Figures 3D-E; pg 49, 54-55, 66-67); the DNA sequence encoding a detoxifying enzyme could be used as a selectable marker. Blowers et al also teach a method for introducing into a tobacco plastid genome a DNA sequence encoding a detoxifying enzyme, wherein the method comprising introducing the vector into a tobacco plastid genome,

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and wherein the transformants were selected on glyphosate, and plants so produced (pg 49-53, 55-57 and 67-72). Seed was collected from the plants and progeny produced (pg 72). The regions of homology to the petunia plastid genome would be "inclusive of" the 5' and 3' ends of "spacer regions".

14. Claims 1-3, 5-6, 18-20, 28 and 30 are rejected under 35 U.S.C. 102(e) as being anticipated by McBride et al (US Patent 6,271,444, filed July 1998).

McBride et al teach plant plastid transformation vectors comprising a region of homology to the tobacco plastid genome, the plastid 16S ribosomal RNA promoter, a ribosome binding site in a 5' untranslated leader, a DNA sequence encoding a detoxifying enzyme (EPSPS, gox, hph, glpA, glpB or bxn), a transcription termination region and another a region of homology to the tobacco plastid genome (Figures 2-3; column 12, line 13, to column 14, line 43; claims 1-12); the DNA sequence encoding a detoxifying enzyme could be used as a selectable marker. McBride et al also teach such plastid transformation vectors wherein the vectors also comprise the protein-encoding genes of interest, aadA, AHAS or cry1Ac (column 14, line 44, to column 15, line 39). McBride et al also teach a method for introducing into a tobacco plastid genome a DNA sequence encoding a detoxifying enzyme, wherein the method comprises introducing the vector into a plant cell, and plants so produced (column 17, line 7, to column 18, line 27; claims 1-12); the method would not require antibiotic selection. Seed is produced in the transformation method (column 18, line 24). The regions of homology to the tobacco plastid genome would be "inclusive of" the 5' and 3' ends of "spacer regions".

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15. Claims 1-28 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maliga et al (1999, US Patent 5,877,402) in view of each of Daniell et al (1994, NATO ASI Series Vol. H 86:589-604) and Ursin (1997, US Patent, 5,633,153, filed October 1994).

The claims are drawn to plastid transformation vectors comprising a DNA sequence encoding a detoxifying enzyme and a method of transforming plastids wherein antibiotic resistance detection is not required.

Maliga et al disclose plastid transformation vectors comprising the plastid *psbA*, *rps16* or *Prrn* promoters and a 5' UTR operably linked to the *aadA* or *uidA* genes, the 3' region of the plastid *psbA*, *rps16*, or *rbcL* genes, and flanking sequences for homologous recombination with the plastid genome (the *rbcL* sequence and the ORF512 sequence or the *rps12* sequence and the 16S rDNA sequence) (Figures 19C-G, 20C-F and 22 A-C; column 56, lines 1-56; column 61, lines 55, to column 63, line 16). Maliga et al also disclose plastid transformation vectors that comprise the *Prrn* promoter operably linked to a kanamycin resistance gene, the 3' region of the plastid *psbA* gene and flanking DNA sequences (Figure 8 and 9E; column 38, line 25, to column 43, line 47). The vectors of Maliga et al also have a ribosome binding site (claims 16 and 24). Maliga et al also teach progeny of the transformed plants (see, eg column 54, lines 58-67). Maliga et al do not disclose use of a BADH gene as a selectable marker.

Daniell et al disclose a method of plastid transformation and vectors comprising the *psbA*, *rbcL* or *atpB* promoters, a DNA sequence encoding an antibiotic resistance gene, termination sequences and a gene of interest (pg 591-592, paragraph 1). Daniell et al also suggest expression of BADH in plastids (pg 598, paragraph 2).

Ursin teaches a method of using BADH genes from spinach, beet or *E. coli* as selectable markers in transformation of a variety of plants, including tobacco, tomato, potato, rice, Brassica, cotton and soybean (column 7, lines 20-55; column 8, lines 55, to column 9, line 67; claims 1-21). The method involves selection of cells comprising the DNA encoding BADH and regenerating those cells into plants (column 7, lines 20-55). The protein is targeted to the chloroplasts (column 5, lines 17-41) and the resulting plants are resistant to betaine aldehyde (column 10, lines 1-27).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the plastid transformation vectors, methods of plant transformation, and plants transformed therewith as taught by Maliga et al, to express BADH in the vectors and to select for BADH-expressing transformed plant cells as described in Ursin. One of ordinary skill in the art would have been motivated to do so because of the suggestion of Daniell et al to do express BADH directly in plastids and because Ursin et al teaches the use of BADH as a selectable marker.

Applicant's arguments filed 9 January 2003 and 24 March 2003 to a rejection of claims 1-12, 14-17, 19-28 and 30 under 35 USC 103 (a) as being unpatentable over Maliga et al in view of Ursin are addressed to the extent they pertain to the instant rejection.

It is noted that Applicant incorrectly lists the rejected claims in the response (responses, 9 January 2003, pg 20 and 24 March 2003, pg 18).

Applicant urges that Ursin teaches a method of using an aldehyde dehydrogenase as a selectable marker for nuclear transgenic plants and teaches away from chloroplast expression of BADH by suggesting altering the gene for expression of BADH in the cytoplasm for higher

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selection efficiency. Furthermore, Ursin teaches use of a BADH enzyme that lacks a transit peptide and suggests deletion or destruction of the transit peptide. Applicant also urges that Ursin teaches that an 8 amino acid transit peptide is not adequate for targeting BADH to the chloroplast (responses, 9 January 2003, pg 20-21 and 24 March 2003, pg 18-19).

This is not found persuasive because Ursin's teachings are merely for higher selection efficiency; it is noted that unmodified plant BADH genes were effective for selection at a wide range of betaine aldehyde concentrations (Ursin, Table 3). Ursin does not teach that an 8 amino acid transit peptide is not adequate for targeting BADH to the chloroplast, but merely teaches that such a transit peptide is atypical and that the targeting mechanism for plant BADHs is unknown, even though they are transported to the chloroplast (see the paragraph quoted by Applicant). Ursin teaches the effectiveness of BADH as a selectable marker in tobacco (column 8, lines 55, to column 9, line 67)

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant urges that nuclear BADH has a high GC content and codon usage and could not be expected to be expressed well in AT-rich plastid compartments; thus, it would not be obvious to express a nuclear gene in a prokaryotic[-like] plastid (responses, 9 January 2003, pg 21, and 24 March 2003, pg 19).

This is not found persuasive because Maliga et al suggests expression of a variety of nuclear genes, including insulin, EPSPS, ALS and bar, in the plastid (column 27, line 14, to

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column 28, line 10). It is also noted that a great variety of nuclear-encoded eukaryotic genes have been successfully expressed in a variety of prokaryotes; one of ordinary skill in the art would expect that nuclear-encoded genes could also be expressed in a prokaryote-like plastid. Furthermore, Ursin teaches selection with the *E. coli* BADH gene (claims 6 and 15), which would have a prokaryotic codon usage.

Conclusion

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at (703) 308-0198.

Anne R. Kubelik, Ph.D.

June 12, 2003

